Nevertheless, Level 1 evidence on routine use of PSA testing in the elderly is lacking because men aged > 75 years were not included in major screening trials.[10,11] According to the 2011 US National Vital Statistics, the average man is expected to live an additional 14.3 years at age 70, and 11.0 years at age 75.[12] Although overdiagnosis and overtreatment clearly can cause harm in this expanding population, our challenge is to also avoid undue morbidity and mortality from underdiagnosis and undertreatment of elderly men. ■

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PSA Velocity in Risk Stratification of Prostate Cancer

Reviewed by Marc A. Bjurlin, MD, Stacy Loeb, MD
Department of Urology, New York University and the Manhattan Veterans Affairs Hospital, New York, NY

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Since the introduction of widespread prostate-specific antigen (PSA)–based prostate cancer screening, several markers have been employed to aid in detection of prostate cancer. The change in PSA level over time, PSA velocity (PSAV), is such a marker that may improve specificity; however, its role as an adjunct to PSA is controversial. Some prior studies have shown that a PSAV provides independent predictive information for estimating prostate cancer risk[1] and a PSAV threshold of 0.35 to 0.4 ng/mL/year has been associated with the likelihood of insignificant prostate cancer, suggesting that PSAV may increase specificity for identifying patients with clinically significant disease.[2,3] Conversely, other studies have shown that PSAV has limited value[4] and biopsying men with high PSAV but no other indication would lead to a large number of additional prostate biopsies.[5] Recently, Ørsted and colleagues[6] and Wallner and associates[7] evaluated the value of PSAV as an adjunct marker to PSA, its role in predicting aggressive disease, and improving classification of prostate cancer risk and mortality.

Long-term Prostate-specific Antigen Velocity in Improved Classification of Prostate Cancer Risk and Mortality

Ørsted DD, Bojesen SE, Kamstrup PR, Nordestgaard BG.
Eur Urol. 2013;64:384-393.

Ørsted and colleagues reported on whether long-term PSAV improves classification of prostate cancer risk and mortality. Among 7455 men in the Copenhagen City Heart Study, they identified 503 men (121 with prostate cancer; 382 matched control subjects) aged 30 to 80 years with repeated PSA measurements taken over 20 years. The goals of the study were to examine individual changes in PSA over a long time interval, and determine whether these changes were associated with prostate cancer risk and mortality beyond what is predicted by total PSA. Their findings were then applied to the general male population aged 40 to 80 years living in Denmark from 1997 through 2006 (n = 1,351,441).

Virtually all study participants were white Danish men, and the median age at baseline was similar for men with prostate cancer and those without it (age 68 and 69 years, respectively). The absolute and relative long-term PSAV increased continuously as a function of time from > 20 years earlier up until prostate cancer diagnosis in cases compared with matched control subjects ($P = .002$ and $P = .001$, respectively).

On multivariable analysis, PSAV > 0.35 ng/mL/year was associated with a 5.3-fold increased risk of prostate cancer and a 3.4-fold increased risk of disease-specific death after controlling for PSA. Similarly, when expressed as a percent change, a long-term PSAV > 10% was associated with a 2.7-fold increased risk of diagnosis, but a nonsignificant 2.2-fold increased risk of prostate cancer death in the model with PSA.

The authors did not find a statistically significant increase in area under the curve (AUC) using kinetic measurements in addition to PSA, although the use of

receiving operating characteristic (ROC) analysis for this purpose has been criticized.[8] Thus, the authors proceeded to report net reclassification analysis to determine whether PSAV reclassified the risk of prostate cancer diagnosis and mortality. This analysis revealed that adding long-term PSAV to models already including baseline PSA values and age resulted in statistically significant net reclassification, although the emphasis on continuous net reclassification analysis in this study has been questioned.[9] Instead, using an arbitrary threshold of 5% risk of 10-year mortality, PSAV did not significantly reclassify events, but led to significant reclassification of nonevents.

Overall, the study has several strengths and limitations. The study population was representative of the general population of men, well-characterized, with long (28 years) and complete (100%) follow-up. Limitations included a homogeneous cohort that mainly included white participants of Danish descent who had only two or three PSA values over such a long period. In most studies with PSA measurements taken $\geq$ 4 years apart,[10,11] PSA kinetics measurements were less predictive than in studies where PSA kinetics were calculated from PSA measurements drawn 1 to 2 years apart,[12,13] as the metric was originally described. Furthermore, some men may have been diagnosed with prostate cancer or died after their first examination, which may have excluded men with the most aggressive cancers.

Nevertheless, these data suggest that long-term PSA changes may be useful in identifying men with a low probability of prostate cancer mortality, and, as a result, may ultimately reduce unnecessary prostate biopsies. However, we need to determine the optimal interval between PSA measurements and method of kinetics calculation for clinical use. Furthermore, whether prostate cancer is curable at the point when PSAV indicates intervention is of key importance. The majority of study participants with PSAV $>$ 0.35 ng/mL/year and/or $>$ 10% per year had PSA levels $<$ 10 ng/mL, suggesting probable detection within the window of curability.

Changes in Serum Prostate-specific Antigen Levels and the Identification of Prostate Cancer in a Large Managed Care Population

Wallner LP, Frencher SK, Hsu JW, et al.
BJU Int. 2013;111:1245-1252.

Wallner and colleagues, from Kaiser Permanente in Southern California, determined whether the rate of change in total serum PSA levels accurately detects prostate cancer and whether it adds any predictive value to a single measurement of serum PSA alone. The authors performed a retrospective cohort analysis of 219,388 community-dwelling men, aged $\geq$ 45 years, enrolled in the Kaiser Permanente Southern California health plan from 1998 to 2007. All men had no history of prostate cancer at baseline and underwent at least three PSA measurements. The authors evaluated the annual percent change in total serum PSA levels, and determined the accuracy of PSA changes for overall prostate cancer detection as well as detection of Gleason $\geq$ 7 disease compared with a single PSA measurement.

A total of 10,035 men developed prostate cancer during the study period. These men were slightly older, more likely to be African American, and had shorter follow-up times when compared with men who did not develop prostate cancer (all $P < .001$). Men in this study received approximately five PSA tests during the study period and the mean number of PSA tests was marginally higher among men who developed prostate cancer (5.32 tests) compared with men who did not (5.28 tests; $P = .002$).

In the overall study population, the mean change in PSA levels was 2.9% per year and the rate of change in PSA increased modestly with age ($P < .001$). Overall, men who developed prostate cancer experienced a more rapid percent change in PSA per year than men who did not ($P < .001$). Moreover, the authors reported that annual percent changes in PSA accurately predicted the presence of prostate cancer (AUC = 0.963) and aggressive disease (AUC = 0.955), representing greater predictive accuracy for aggressive disease than a single measurement of PSA alone (AUC = 0.727). Furthermore, the combination of PSA and PSA velocity did not improve the accuracy of prostate cancer detection beyond that of PSA velocity alone.

There are several strengths of this study including its large sample size, with considerable follow-up, and a large retention rate ($>$ 80%). Previous studies evaluating PSAV have relied on the absolute changes in PSA over time, whereas the current study evaluated the annual percent change in PSA, which the authors suggest may be a more accurate measure of PSAV. It would be interesting to assess how this metric compares with PSAV risk count, which has previously been shown to improve the identification of clinically significant disease.[13]

A major limitation of the study by Wallner and colleagues is that not all men in the study underwent a prostate biopsy during follow-up, which introduces a verification bias. The study did not control for the

surgical and medical management of benign prostatic hyperplasia and its effects on PSA levels. Three PSA assays were used throughout the study period which may result in pseudoacceleration or pseudodeceleration.[14] Furthermore, the study registry did not capture prostate cancer diagnoses that occurred after membership termination. Finally, concern has been expressed about inconsistency between the data presented in the figures and text, which requires additional clarification.[15]

Discussion

Contrary to what has been previously suggested,[15] no randomized trial has evaluated the outcomes of a screening program based on PSA kinetics. Each of the many observational studies and secondary analyses of PSAV has important drawbacks. However, the absence of evidence is not evidence of absence.[16] If confirmed, the studies of Ørsted and colleagues[6] and Wallner and associates[7] will add to the growing body of literature supporting the value for PSA kinetics in improving detection beyond that of a single baseline PSA measurement. In particular, these studies suggest that PSAV may be useful when screening for aggressive disease, with the goal of ultimately reducing unnecessary prostate biopsies and overdiagnosis. Additional prospective evaluation is necessary to confirm that PSAV may identify men at a time point when their disease is curable and may benefit from curative intervention. ■

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Patient Perceptions and Shared Decisions About PSA Screening

Reviewed by Daniel Wollin, MD, Stacy Loeb, MD
Department of Urology, New York University and the Manhattan Veterans Affairs Hospital, New York, NY

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The past few years have witnessed a rapidly changing panorama regarding recommendations for prostate cancer screening. At one extreme, the United States Preventive Services Task Force (USPSTF) issued a grade D recommendation against prostate-specific antigen (PSA) screening.[1] Meanwhile, most other groups recommend shared decision making about screening, including a discussion between patients and physicians about the associated controversies and taking into consideration patient preferences.[2] For example, the American Urological Association (AUA) recently issued new guidelines supporting shared decision making about PSA testing for average-risk men aged 55 to 69 years, while opposing PSA testing as part of health fairs and other community settings in which shared decision making is not part of routine practice.[3] Two recent studies have attempted to quantify the effect of these changing recommendations on patient perceptions and patient-physician discussions regarding PSA screening.

National Evidence on the Use of Shared Decision Making in Prostate-Specific Antigen Screening

Han PK, Kobrin S, Breen N, et al.
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Proper shared decision making between a patient and physician involves several components, including a discussion of the advantages, disadvantages, and scientific uncertainties. The goal of this study was to assess the extent to which shared decision making is actually used for PSA screening decisions and its implications.